UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,161	03/31/2004	Richard Daifuku	021227-000410US	9045

20350 7590 09/20/2005

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,161	DAIFUKU ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-31 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected as it dependent on a rejected claim and shares the same indefiniteness.

1. Recitation of " R^2 is a member selected from (=O) or NR^7R^8 " in claim 1 renders claim 1 and its dependent claims 2-31 indefinite for more than one reason. First of all as recited the carbon bearing R^2 has a hydrogen and R^2 is a monovalent group. Hence R^2 cannot be =O. Secondly, as recited the NR^7R^8 choice is a monovalent group and hence if R^2 is divalent, then the valence of nitrogen will be more than three and there is recitation as to what else is appended to the nitrogen to make it a pentavalent. Furthermore, reading rest of the claims it appears that NR^7R^8 can be NH_2, NHOH etc., which would preclude pentavalent nitrogen. Thus structural make-up of the compound of formula I is unclear and hence a proper prior art search cannot be done.

In addition, the proviso in claim 1, renders claim 1 and its dependent claims indefinite as none of the said substituents are carbamate or urea. Hence, it is not clear what is intended and this proviso is not applicable.

2. Claim 31 is indefinite as it recites compound according to formula I but has no structural formula o. Note the dependency of the claim is not defined. An appropriate correction is needed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of HIV viral infection, does not reasonably provide enablement for any or all viral diseases or any or all cancers including those yet to be discovered as due the mode of action of instant triazine compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to "treating a viral disease" and "treating cancer" by providing a prodrug analog of nucleoside. The scope of the claims includes any or all cancer or any or all viral diseases including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of the claims includes treatment of various viral diseases due to DNA virus such as hepatitis B virus, herpes viruses (e.g., Herpes Simplex Virus, Cytomegalovirus (CMV), Epstein-Barr

Virus, (EBV)), smallpox virus, or human papilloma virus (e.g., HPV), many human and animal pathogens: flaviviruses, such as dengue fever, West Nile, and yellow fever; pestiviruses, such as bovine viral diarrhea (BVD), and hepaciviruses, such as hepatitis C; filoviruses such as ebola; parainfluenza viruses, including respiratory syncytial; rubulaviruses, such as mumps; morbillivirus, such as measles, picomaviruses, including the echoviruses; the coxsaclçieviruses; the polioviruses; the togaviruses, including encephalitis; coronaviruses, including Severe Acute Respiratory Syndrome (SARSI; rubella; bunyaviruses; reoviruses, including rotaviruses; rhabdoviruses; arenaviruses, such as lymphocytic choriomeningitis, as well as other RNA viruses of man and animal and various cancers including neoplastic disorders of hematopoietic stem cells, leukemias such as adult and pediatric acute myeloid leukemias (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), hairy cell leukemia and secondary leukemia, specific leukemias include acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, aleukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic

leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, plasmacytic leukemia, promyelocytic leukemia, meder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, and undifferentiated cell leukemia, lymphomas such as non-Hodgkin's lymphoma (NHLI and Hodgkin's disease., other hematological malignancies include myelodysplastic syndromes (MDS), myeloproliferative syndromes (MPS) and myelomas, such as multiple myeloma and solitary myeloma, multiple myeloma etc., which is not adequately enabled solely based on the activity of the compounds provided in the specification at 28 and 45-48.

The instant compounds are disclosed to act by nucleotide analog resulting in gradual accumulation of random mutations in the viral genome leading to gradual inactivation of potentially any of the viral proteins with less selective pressure and it is recited that the instant compounds are therefore useful in treating any or all disorders, for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action that would be useful for all sorts of viral diseases and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases viral disease and cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs with distinct mode of action.

The scope of the claims involves millions of compounds of claim 1 as well as the thousand of diseases embraced by the terms disorder, viral disease and cancer.

In addition, claim 21 is deemed as reach through claim wherein a mode of action is recited first and then all or any diseases that relate to the mode of action is claimed. In the instant case because of the mode of action as gradual mutation of virus, the instant compounds are implied to be useful for treating any or all viral disease and cancers..

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed

invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Daifuku Biodrugs17(3); 169-177, 2003. and Anderson etal., Annu. Rev. Microbiol., 58:183-205, 2004 (PubMed Abstract provided).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating viral diseases and cancers that require gradual accumulation of random mutations in the viral or tumor cell genome leading to gradual inactivation of potentially any of the viral or tumor cell proteins with less selective pressure.

2) The state of the prior art: Recent publications expressed that the such mutation/ inhibition effects are unpredictable and are still exploratory. See Daifuku and Anderson et al. cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all viral disease and cancer with the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases

involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of such viral inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all viral diseases and cancers. .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6,7 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Wierenga US 4,140,850.

Wierenga teaches 2,2'anhydrotriazine nucleosides for treating herpes virus, which include instant compound. See column 2, formula II. Note when instant R^2= O, R^4, R^6 is OR^3, R^3 is H, compounds taught by Wierenga includes instant compounds. See column7-8, Table II for various compounds made.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Acting Supervisory Patent Examiner (SPE) of the art unit 1624

is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

Venkataraman Balasubramanian

9/3/2005